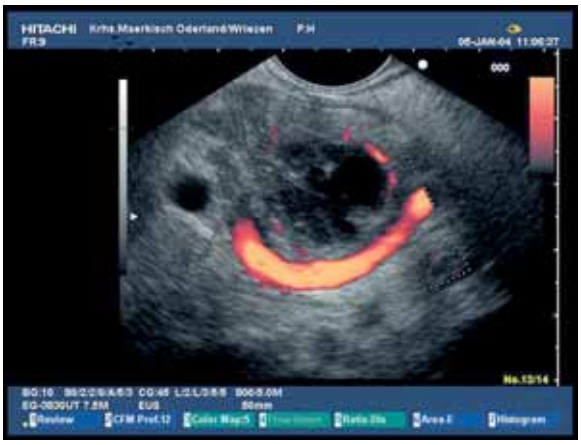

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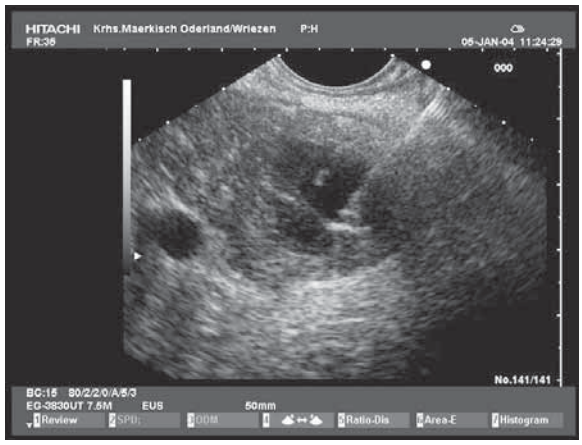

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Fig. 16.29a, b Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in a patient with acute recurrent pancreatitis and a solid cystic mass lesion in the pancreatic tail. Turbid fluid was aspirated. The cytological and histological findings were typical of necrotic changes.

between inflammatory masses, organized necrosis, and neoplastic lesions.[148–153]

EUS-FNA generally has very high levels of sensitivity (80–95%) and specificity (> 90%) for diagnosing adenocarcinoma of the pancreas.[154–156] However, it is not capable of resolving the differential-diagnostic dilemma of hypoechoic mass lesions in patients with chronic pancreatitis. In such patients, the diagnostic sensitivity of EUS-FNA, even in highly specialized centers, has been reported to be between only 44% and 80%[131,135,157–162] (**Fig. 16.29**). Analysis of the K-*ras* point mutation and other molecular-genetic investigations,[161,164–166] as well as new immunohistochemical markers (14-3-3σ, mesothelin)[167] in specimens obtained with EUS-FNA may enhance the diagnostic accuracy in unclear cases.

We recommend that patients with chronic pancreatitis and a focal hypoechoic, hypoperfused lesion should be referred for surgery without delay if the clinical and imaging findings strongly suggest the presence of a resectable adenocarcinoma. Patients with chronic pancreatitis in whom CCDS shows a well-perfused lesion and in whom the CA19-9 level is low should undergo EUS-guided biopsy.[156] If this shows findings typical of chronic pancreatitis or autoimmune pancreatitis, we would suggest that as an alternative to surgery the patient might want to undergo further follow-up examinations, at least in the short term. One very recent study suggests that combining CE-EUS, EUS elastography and EUS-FNA is very promising for the differential diagnosis between chronic pseudotumoral pancreatitis and pancreatic cancer[168]. In our own experience, we have found that CE-EUS and EUS elastography help define the margins of the suspicious tumor, facilitating targeting of the lesion and thus increasing the diagnostic yield in patients with chronic pancreatitis and suspected adenocarcinoma (**Figs. 16.28** and **16.30**).

Pseudocyst versus Simple Cyst versus Cystic Neoplasia versus Pseudoaneurysm

If CCDS is used, it is relatively easy to differentiate between cystic lesions and pseudoaneurysms, both with US and with EUS (see **Fig. 16.17**). With mechanical radial echoendoscopes, this differentiation is not possible in some cases.

However, it is much more difficult—although extremely important, from the point of view of prognostic assessment and treatment—to differentiate between pseudocysts (80–90% of cystic pancreatic lesions), simple nonneoplastic cysts, and benign or malignant cystic neoplasms (serous or mucinous cystadenoma; mucinous cystadenocarcinoma; intraductal papillary mucinous tumors: ≈ 10–20% of cystic lesions in the pancreas) (**Fig. 16.31**; see also **Figs. 16.33** and **16.36**).

Lesions that occur only very rarely include cystic islet cell tumors, cystic lymphangiomas, solid pseudopapillary tumors, cystic teratomas, and paragangliomas or ganglioneuromas.[169–173] The incidence of pancreatic cystic lesions is much higher than previously reported. The widespread use of modern high-quality cross-sectional imaging and ultrasound has dramatically increased the number of patients in whom asymptomatic pancreatic cysts are discovered incidentally.[20,169,174]

A Japanese group have presented an endosonographic classification of cystic pancreatic lesions, consisting of six morphological subtypes: thick wall type; protruding tumor type; thick septal type; microcystic type; thin septal type; and simple type. Retrospectively, they were able to achieve reliable differentiation between neoplastic and nonneoplastic cystic pancreatic lesions using this classification.[175] A similarly reliable method of differentiation (with a sensitivity of 92%), which is only based on morphological criteria, has been presented by a group at the Mayo Clinic. They found that a wall thickness of 3 mm or

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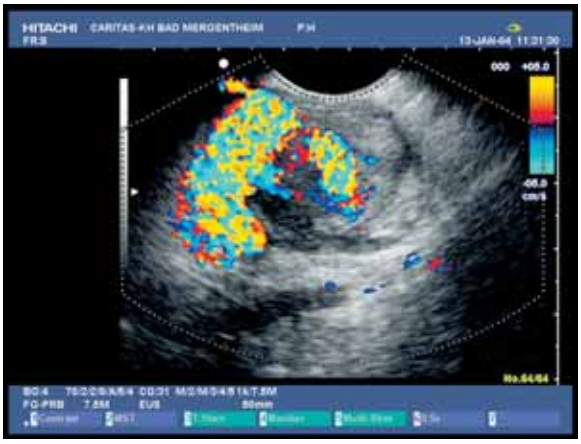

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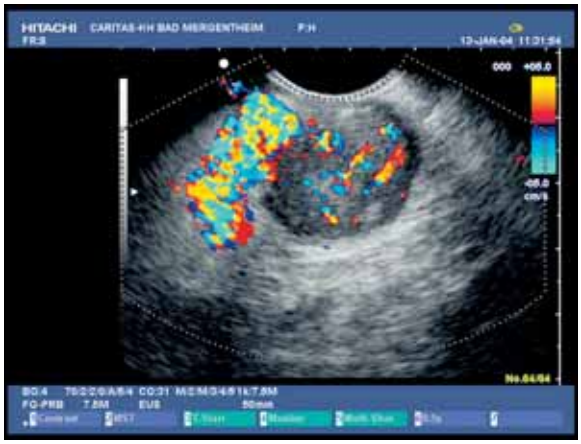

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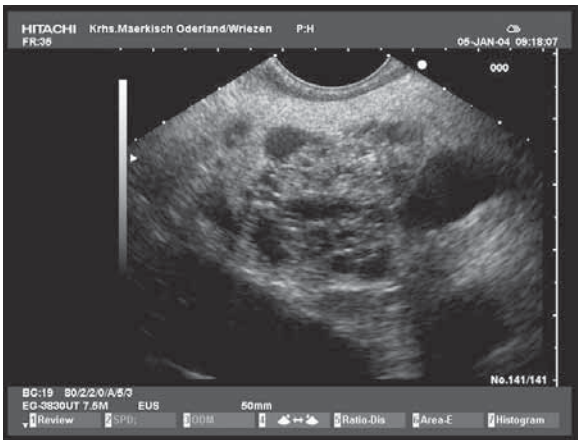
Fig. 16.30a–e A hypoechoic mass in the pancreatic tail, suspected to be adenocarcinoma.
a Color-coded duplex endoscopic ultrasound clearly delineates the splenic artery next to the mass lesion, but demonstrates no perfusion inside the lesion.
b–e Following intravenous injection of the contrast-enhancing agent SonoVue, several vascular signals are identified inside the lesion. After surgical resection, the histological examination excluded adenocarcinoma (the ultimate diagnosis was chronic pancreatitis).



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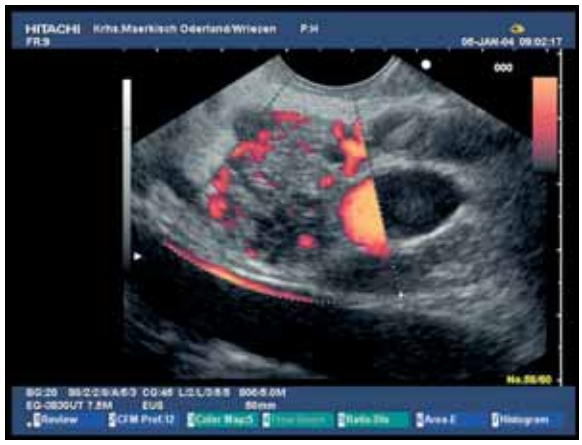

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Fig. 16.31a, b Cystic mass lesions in the pancreas (serous microcystic adenoma).

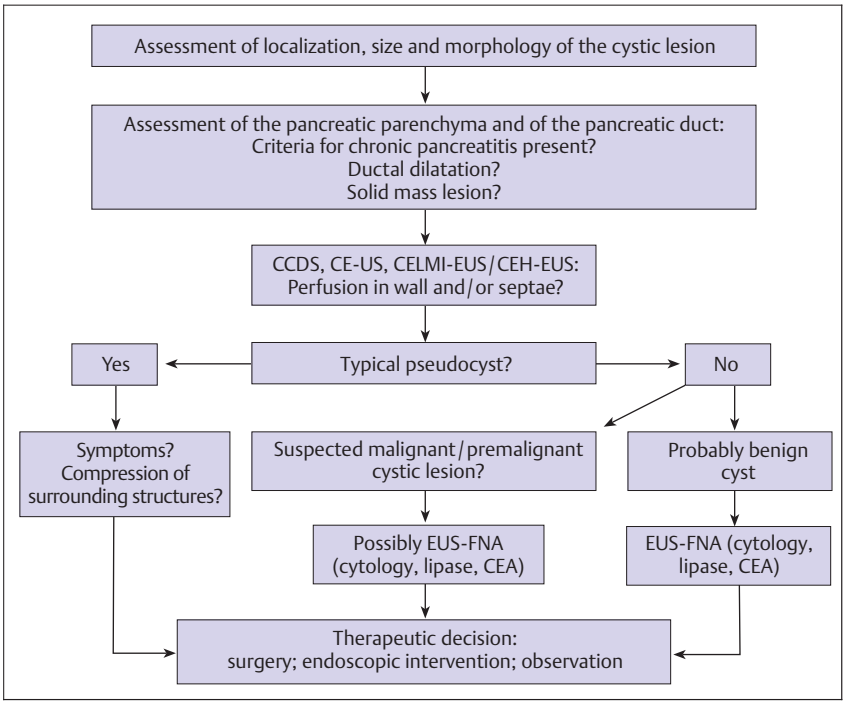


Fig. 16.32 Flow chart for the differential diagnosis of cystic lesions of the pancreas. CCDS, color-coded duplex sonography; CE-EUS, contrast-enhanced endoscopic ultrasound; CELMI-EUS, contrast-enhanced endoscopic ultrasound with low mechanical index; CEH-EUS, contrast-enhanced harmonic endoscopic ultrasound.

greater, macroseptation (all cyst compartments > 10 mm), the presence of mass or intratumoral growth, and cystic dilation of the main pancreatic duct were criteria for malignancy.[172] Similarly, Gress et al.[176] suggested that solid cystic or complex cystic mass lesions were typically malignant. Intraductal mucinous adenocarcinomas may sometimes also have hyperechogenic foci inside the solid part.[176] On the other hand, considerable interobserver disagreement has been reported among eight experienced endosonographers with regard to the diagnosis of neoplastic versus nonneoplastic cystic lesions, the specific type, and the specific EUS features of cystic pancreatic lesions.[177]

Small incidental simple pancreatic cysts that have initially been classified as benign do not undergo malignant change or cause morbidity or mortality, even if followed up for a long period.[178–180] There have been several prospective studies of cystic pancreatic lesions before surgical removal. In contrast to earlier studies, they found that several criteria—e.g., wall thickness, presence of septa, presence of solid parts, and lymphadenopathy—were not sufficiently reliable to differentiate between benign and malignant lesions if the patient's clinical history and the morphology of the pancreatic parenchyma were not known.[181–183] The sensitivity of diagnosing malignant and/or premalignant mucinous cysts can be increased by

Table 16.7 Morphological, cytological, and biochemical criteria for different cystic lesions of the pancreas. Data from [168–177,181–191,196–212,214–217]

Cystic lesion	EUS morphology	Cyst content and cytology	Biochemistry
Serous cystadenoma (SCA)	Microcystic, rarely macrocystic; thin septa, blood vessels within the septa	Thin, translucent fluid; small, cuboid epithelia containing glycogen	Lipase usually low; CEA low (< 5 ng/mL)
Mucinous cystadenoma (MCA)	Macrocystic, thick septa, thick wall, potentially intramural tumor	Viscous fluid; fluid stains positive for mucin; mucinous columnar epithelial cells with variable atypia	CEA high: > 192 ng/mL [183] > 400 ng/mL [184] > 480 ng/mL [190] > 800 ng/mL [188] Predictive of malignancy: CEA > 6000 ng/mL [190]
Intraductal papillary mucinous neoplasia (IPMN)	Dilation of the duct without stricture (main duct type), communication of cystic structures with MPD or side branches (branch duct type), probably non-anechoic contents and mural nodules, variable morphology Indicators of malignancy: • Cystic components > 30 mm • Dilated MPD • Solid components • Mural nodules • Thick septa	Neoplastic mucinous cells: — Entrapped in a mucinous background (thick, colloidlike mucin in ≈ 50%) — Either single or arranged in loosely cohesive sheets, sometimes forming papillary formations IHC: MUC-1, MUC-2 Indicators of malignancy: • Necrosis • Epithelial cell clusters with hyperchromatic nuclei and a high nuclear-to-cytoplasmic ratio • Pale nuclei with parachromatin clearing	CEA variable high Lipase high Predictive of malignant IPMN: • CEA > 120 ng/mL [217] • CEA > 200 ng/mL [203] • CEA > 2500 ng/mL [206] • CA 72.4 > 40U/mL [203]
Pseudocyst	Simple cyst or cyst with thin septa, sometimes echogenic debris; changes in the pancreatic parenchyma	Thin, muddy-brown fluid; negative fluid staining for mucin; histiocytes, macrophages, neutrophils, but no epithelial cells	Lipase +++; CEA low (usually < 5 ng/mL)
Simple cyst	Simple cyst or cyst with thin septa	Epithelial cells; no atypical cells	Lipase variable; CEA low
Cystic neuroendocrine tumor	Solid tumor with a large unilocular cyst	Thin, sometimes bloody fluid; monomorphic endocrine tumor cells, staining positive for chromogranin A and synaptophysin	No data
Solid pseudopapillary tumor (SPT)	Well-defined echo-poor (solid, mixed solid-cystic or cystic) tumor mainly of the pancreatic tail or body	Bloody fluid, sometimes with necrotic debris; monomorphic cells with round nuclei and eosinophilic, foamy cytoplasm with large, clear vacuoles; branching fragments with central capillaries and myxoid stroma; IHC: vimentin, α1-antitrypsin, α1-antichymotrypsin	No data

CA, cancer antigen; CEA, carcinoembryonic antigen; IHC, immunohistochemistry.

using a combination of endosonographic morphology, cytology of the fluid within the cyst, and the level of carcinoembryonic antigen (CEA)[170,171,173,174,183–191] (**Fig. 16.32**; **Table 16.7**). Measuring the CEA level in the fluid within the cyst has been found to be superior to measuring other tumor markers. However, there is considerable overlapping of CEA levels between the various types of pancreatic cystic lesion. The CEA cut-off levels reported in different studies vary substantially. CA19-9 may be nonspecifically raised in inflammatory processes.[173,188] The presence of high levels of pancreatic enzymes is typical of pseudocysts, but may also occur in cystic neoplasms that communicate with the pancreatic ducts.[173] In selected cases, injecting secretin during EUS may be useful for differentiating small cystic lesions of the pancreas; this causes enlargement of pseudocysts that communicate with the pancreatic duct, but cystic neoplasms do not change in size.[192]

In the future, molecular analysis of DNA mutations in pancreatic cyst fluid may be helpful in the difficult differential diagnosis of cystic lesions of the pancreas.[193–195] In addition to biochemical, cytological, and molecular-genetic evaluations of the cystic fluid and other cost-intensive tests, we consider that morphological assessment of the entire pancreas and consideration of the clinical background (e.g., whether the patient has previously had episodes of acute pancreatitis or has a history of alcohol abuse) need to be taken into account and may well be more important[11,173,185–187] (**Fig. 16.32**).

Fig. 16.33 Aspiration of a macrocystic adenoma of the pancreas.

However, it is important to remember that intraductal papillary mucinous neoplasms (IPMNs) may present with acute recurrent pancreatitis[196] and are accompanied by features of chronic pancreatitis in a high percentage of patients.[197] Doing without further investigation of a cystic pancreatic lesion is only acceptable if the clinical context, the (endo-)sonographic morphology of the pancreas and of the cystic lesion, and the findings of any other imaging examinations are taken into account, and if the lesion appears typical of a pseudocyst. If the diagnosis of a pseudocyst is uncertain, or if a cystic neoplasm is suspected, it depends on the degree of diagnostic uncertainty whether, before proceeding to surgery, the clinician may wish to undertake EUS-FNA of the contents of the cyst for cytological and biochemical studies[155–157,173,174,183–190,193–195,198–212] (**Table 16.7**; **Fig. 16.33**).

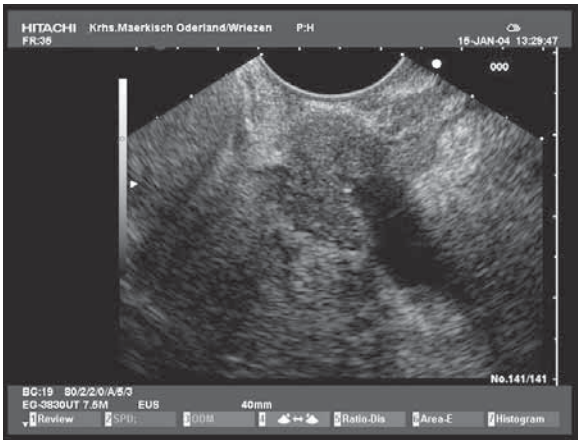
In the case of EUS-FNA of cystic pancreatic lesions, antibiotic prophylaxis is mandatory.[171] The age of the patient is also an independent risk factor for malignancy and should be considered when making therapeutical decisions. However, the decision on whether to carry out surgical resection of a pancreatic cystic lesion has to weigh up the risk of surgery against the risk of malignancy.[173,174]

Dilation of the Main Pancreatic Duct

Dilation of the main pancreatic duct and its branches is one of the classical endosonographic characteristics of chronic pancreatitis and usually occurs together with an irregular, hyperechogenic duct contour.[9,40,50–52,67] In elderly people, mild dilation of the pancreatic ducts without any changes in the duct contour is frequent and can be regarded as normal[9,43] (see **Fig. 16.11b**). If the duct is clearly dilated, it is always necessary to look for an underlying tumor at the papilla or in the pancreatic head. Endoscopic ultrasound is the most suitable diagnostic method here[213] (**Fig. 16.34**).

In a large series of patients with pancreatic cancer who were studied prospectively for the presence of characteristics of chronic pancreatitis, a dilated pancreatic duct was present in just over half of the patients[116] (see **Fig. 16.25**). If the common bile duct and the pancreatic duct are both dilated from the level of the papilla, the differential diagnosis also includes benign stenosis of the papilla, adenomyomatosis, or obstruction by a stone[213] (**Fig. 16.35**, see also **Fig. 16.21**).

A further important differential diagnosis is an intraductal papillary mucinous neoplasm (IPMN). IPMNs are characterized by cystic lesions connected to the MPD (MD-IPMN) or branch ducts (BD-IPMN), with or without small polypoid structures in the wall of the pancreatic duct or cyst, duct dilation, and possibly solid lesions[171,173,196–208,214–217] (**Fig. 16.36**). Mural nodules, cystic components > 30 mm, marked dilation of the MPD, solid components, and thick septa are indicators of malignancy.[214–217] In such cases, endosonography-guided aspiration of the pancreatic duct with antibiotic protection (e.g., ciprofloxacin for 5 days, starting with the intervention), with biochemical and cytological investigation of the



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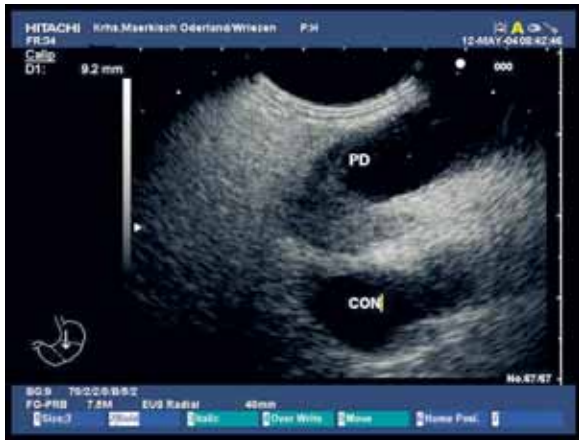

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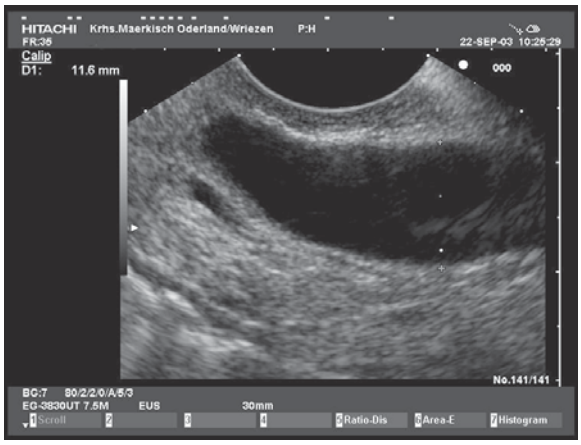
Fig. 16.34a, b Obvious dilation of the pancreatic duct in the presence of tumors of the papilla. CON, portal confluence; PD, pancreatic duct.



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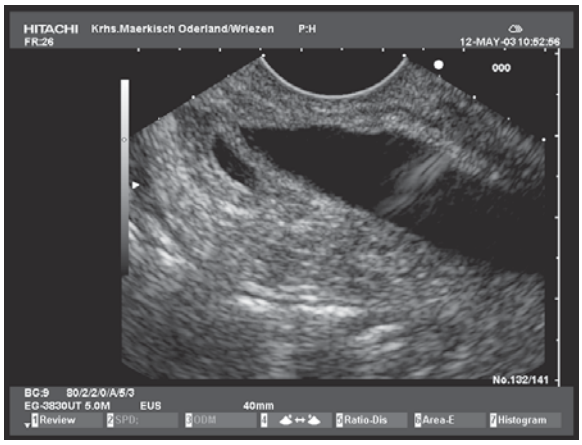

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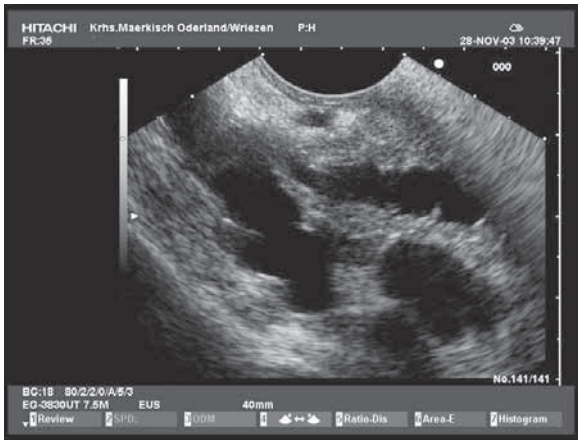
Fig. 16.35a, b Benign stenosis of the papilla.



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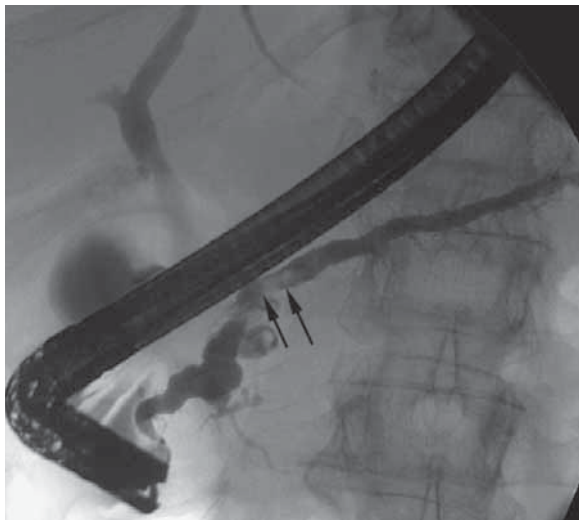

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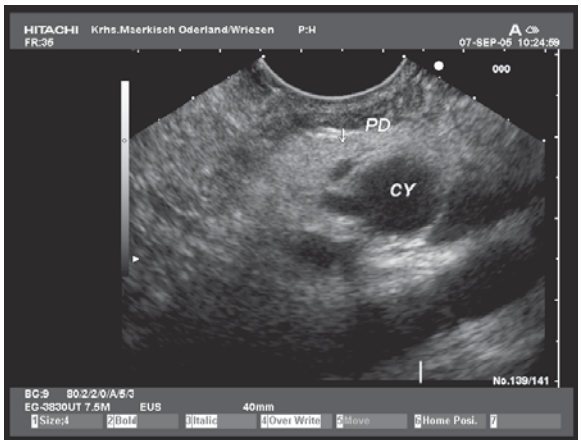

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Fig. 16.36a–d Intraductal papillary mucinous tumors (IPMTs) of the pancreas.
a The corresponding EUS view of an IPMT of the main duct type.
b The corresponding ERCP view. There is obvious dilation of the pancreatic ducts, a bizarre pattern in the absence of any stenosis (endoscopic appearance of a fish-mouth papilla), and indistinct intraductal filling defects (arrows).
c, d An IPMT of the branch duct type. There is marked dilation of the smoothly outlined main pancreatic duct (**c**, color-coded: portal confluence). A small cystic (CY) lesion in the pancreatic body, communicating with a dilated side branch of the main pancreatic duct (**d**, PD).

Table 16.8 Endoscopic ultrasound (EUS)-guided therapeutic interventions in chronic pancreatitis[218–224,233–236]

EUS-guided intervention	Efficacy	Complications
EUS-assisted/guided pancreatic pseudocyst drainage	Several case series (≈ 400 patients) with high technical success (84–100%) and long-term clinical success (80–97%)	0–18% (bleeding, stent migration or occlusion, pseudocyst infection, pneumoperitoneum, perforation and peritonitis), safe also in cases of portal hypertension[233]
EUS-guided transmural necrosectomy and drainage of pancreatic necrosis/abscess	Several case series (more than 250 patients) with high technical success (77–100%) and long-term clinical success (80–93%)	0–31% (bleeding, stent migration or occlusion, pseudocyst infection, pneumoperitoneum, gallbladder puncture, perforation and peritonitis, air embolism) mortality up to 7.5% at 30 days[224]
EUS-guided celiac plexus block/neurolysis	Several case series, retrospective and prospective (controlled) studies with moderate clinical success 59.45% (95% CI, 54.51 to 64.30) (data from meta-analysis of 9 studies with 376 patients: Puli et al. 2009[221]) Benefit diminishes with time EUS-guided celiac plexus block is more effective than CT-guided celiac plexus block in controlling pain in patients with chronic pancreatitis[234,235]	1.6% (major 0.5%)[a]–8.2% (major 0.6%)[b] (self-limited hypotension and diarrhea, retroperitoneal abscess, self-limited postprocedural pain, retroperitoneal bleeding)[236]
EUS-assisted or EUS-guided pancreatic duct drainage	5 case series (92 patients) with moderate-to-high technical (25–92%) and clinical success (69–78%)	14–25% (pancreatitis, bleeding, infection, pseudocyst, perforation)

[a] Complication rate of EUS-guided celiac plexus block in the prospective study by O'Toole and Schmulewitz (2009), n = 189 procedures.[236]
[b] Pooled complication rates of EUS-guided celiac plexus block in 6 studies (n = 170 procedures).[236]

Table 16.9 Diagnostic issues to be considered before endoscopic ultrasound (EUS)-guided or endoscopic drainage of a pancreatic pseudocyst

Is the lesion a typical pancreatic pseudocyst, or could the differential diagnosis include a cystic neoplasm, a pseudoaneurysm, or other benign cystic lesions?
Are the symptoms the patient is presenting with most likely due to the pseudocyst? (Size and location, anatomical relation to other structures, possible compression of neighboring structures)
Are there any diagnostic hints that the pseudocyst may be communicating with the pancreatic duct?
What is the location of the pseudocyst in relation to the wall of the stomach and the duodenum?
Is the pseudocyst (or post-pancreatic abscess) located in a parenchymal organ (spleen, liver)?
How thick is the wall of the pseudocyst? Are there blood vessels within the wall of the pseudocyst or within any septa (if present)?
Are there blood vessels or normal pancreatic parenchyma located between the pseudocyst and the gastrointestinal wall that might be injured during an aspiration?
Is left-sided portal hypertension present, for example with gastric varices?
Does the pseudocyst contain solid structures (sequestra) or sediment?
Are there clinical or endosonographic markers for a potential infection of the pseudocyst (abscess)?
Is additional exudate or free fluid present?

aspirate, has been found to be a safe method with a moderate diagnostic yield. If solid lesions of the pancreas are also present, these should be aspirated as well.[197–208]

The Contribution of EUS to the Treatment of Chronic Pancreatitis

Endoscopic ultrasonography has added several options and advantages to the armamentarium of therapeutic endoscopy for chronic pancreatitis. There is an expanding role for EUS in the planning and guidance of drainage procedures of pancreatic pseudocysts, abscesses, or infected necroses. Several other EUS-guided interventions in chronic pancreatitis have also recently been developed; **Table 16.8** provides an overview.[218–224]

The decision on whether to carry out EUS-guided or endoscopic drainage of a pancreatic pseudocyst depends on several different issues. Clinical and endosonographic findings, as well as potentially the findings of other investigations, influence which interventional method and specific methodology will be used (**Table 16.9**). For example, the interventional methods may differ depending on whether a pseudocyst, an infected pseudocyst, or necrotic tissue is present[222,223] (**Fig. 16.37**).

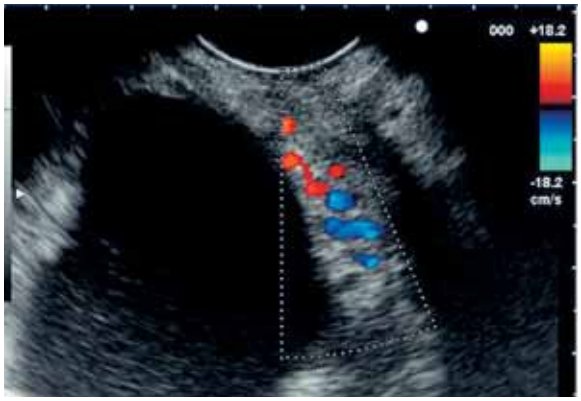

Fig. 16.37 Collateral vessels located between the wall of the pseudocyst and the stomach wall.

In a prospective study of 32 patients who were scheduled to undergo endoscopic drainage of a pancreatic pseudocyst, the endosonographic findings changed the therapeutic plan in more than one-third of the cases.[225] In our experience, one question that remains difficult to answer with endoscopic ultrasound is whether a pseudocyst is communicating with the pancreatic duct. We would therefore recommend that before endosonographic or endoscopic drainage of a pseudocyst, ERCP should be performed, providing the option of transpapillary drainage (**Fig. 16.38**).

Endoscopic ultrasound may also be helpful in planning other therapeutic interventions for chronic pancreatitis, particularly if ERCP is negative or shows an interruption of contrast within the duct during endoscopic retrograde pancreatography. In such cases, it is often possible to identify the reason for the interruption of the contrast medium by using endosonography.[226] It may be possible to differentiate between stones in the pancreatic duct and parenchymal calcifications, or to diagnose pancreas divisum. Endosonography can therefore make a useful contribution to the selection and planning of extracorporeal shockwave lithotripsy (ESWL), surgical procedures, aggressive endoscopic interventions, or endosonography-guided drainage procedures in the common bile duct or main pancreatic duct.[218,227] In this context, the findings reported by Catalano et al.[111] are of interest; using dynamic secretin-stimulated endosonography in patients with pancreas divisum and a history of chronic pancreatitis, it was possible to identify patients capable of benefiting from endoscopic stent placement.

In selected patients with negative endoscopic retrograde pancreatography findings, it may be possible to use endosonography to puncture the pancreatic duct and inject contrast medium, thereby making pancreatography possible.[228,229] This technique allows subsequent EUS-guided transmural or EUS-assisted transpapillary drainage of the obstructed pancreatic duct in symptomatic patients in whom endoscopic retrograde access to the obstructed main pancreatic duct is not possible (see **Table 16.8**).[218–220]

Pitfalls

- Marked dilation of the pancreatic duct may be caused not only by chronic pancreatitis, but also by an intraductal mucinous tumor or by an obstructing proximal tumor of the pancreas or papilla (see **Figs. 16.34, 16.35** and **16.36**). Conversely, an obstructing proximal tumor of the pancreas or an IPMN may cause chronic pancreatitis.
- Enlarged lymph nodes may be present in chronic pancreatitis, autoimmune pancreatitis, or acute recurrent pancreatitis. However, they may also represent lymph-node metastases from a pancreatic carcinoma.[133] (see **Fig. 16.27**)
- Extension into neighboring structures is not always a sign of pancreatic cancer. It may also be present in chronic pancreatitis with focal inflammatory changes and in autoimmune pancreatitis.[81,134,136]
- In the presence of chronic pancreatitis, the diagnostic accuracy of EUS-guided biopsy for focal hypoechoic mass lesions or cystic lesions is too low to refrain from surgical intervention in patients with a suspicious lesion who are otherwise surgically fit.[135,157–163,173,174,184,197–212]

Practical Hints

- If the main pancreatic duct is dilated, its whole course, including the papilla, has to be inspected in detail. The examiner should particularly look for tumors at the papilla and near the ampulla, treatable benign obstructions of the pancreatic duct, associated cystic or solid mass lesions, and small protrusions indicating the presence of IPMN (see **Figs. 16.34, 16.35,** and **16.36**).
- If electronic curvilinear or radial echoendoscopes are used, CCDS—possibly with contrast enhancement (CE-EUS)—should always be used to look for thrombotic complications of chronic pancreatitis or acute recurrent pancreatitis (see **Figs. 16.12, 16.13, 16.14, 16.15, 16.16,** and **16.17**), to differentiate between cystic lesions and pseudoaneurysms and/or cavernomas of the portal vein (see **Fig. 16.17**), and possibly to improve the etiological diagnosis of solid or cystic mass lesions (see **Figs. 16.26** and **16.27**).
- In addition, CCDS should be used before endoscopic/endosonographic drainage of pseudocysts to identify interposed gastric or duodenal varices and extragastric collaterals (see **Figs. 16.15, 16.19,** and **16.37**). Exerting too much pressure with the transducer should be avoided.
- In the presence of chronic pancreatitis, the limitations of EUS-guided biopsy in the differential diagnosis of solid and cystic mass lesions should be borne in mind.
- Particular indications for EUS-guided biopsies (EUS-FNA, EUS-TCB) are as follows[156,173]:
  - To increase the probability of excluding malignant/premalignant changes in a lesion which, according to EUS and CE-EUS, is highly likely to be benign (for example, serous cystadenoma, focal inflammatory lesions, hemorrhagic pseudocyst)
  - Patients with a high clinical and endosonographic suspicion of an unresectable adenocarcinoma and/or pancreatic metastases in the presence of chronic pancreatitis (before palliative therapy)
  - Suspicion of borderline lesions (neuroendocrine tumors, mucinous cystadenoma, lymphoma) before surgical intervention or other specific treatment
  - Dilation of the pancreatic duct of unknown etiology (for example, to diagnose IPMN or ampullary neoplasia)